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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,614	04/15/2002	Yahia Gawad	3477.94	5111

20792 7590 03/22/2006

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,614	GAWAD, YAHIA	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-25 and 27-54* is/are pending in the application.

4a) Of the above claim(s) *28-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20-25 and 41-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 1-18, 20-25, 27-54 are currently pending.

2. Claims 28-40 have been withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4-7, 10-12, 14-17, 19, 21-25, 27, 41, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al [US 5,942,407], in view of Doblhofer [US 4,091,277].

With respect to claims 1, Liotta et al teach a method of using an immunoassay device comprises a sandwich arrangement of three, porous matrix layers (FIG. 1A). The first porous layer corresponds to the signal generating zone and is impregnated with a specific antibody (first binding partner) linked with a photoprotein or a suitable enzyme (label) (column 4, lines 65 – column 5, line 2). The second porous layer is the trapping zone, contains immobilized (bound) reference antigen (second binding partner) that is specifically recognized by the antibody in the first porous layer (column 5, lines 1-4). The third layer corresponds to the reporter system zone and contains a light emitting substance or activating agent that reacts with the photoprotein or enzyme linked to the antibody. Liotta et al further teach that the activating agent may be a caged calcium compound (column 13, lines 30-32) immobilized in a support and using ultraviolet light

to activate the compound (column 13, lines 25-35), in order to extend the duration of light emission resulting from analyte detection (column 13, lines 35-40). Liotta et al further teach using a luminometer that is a compact photomultiplier for sensing the light (column 13, lines 49-53). Liotta et al, however do not teach resetting the photomultiplier after the pulse.

Doblhofer, however, teaches a method of measuring photon events such as electroluminescence (column 40-45), wherein the integrating circuit of the photomultiplier tube is disabled when no photon events are expected, such that the integrator is connected only when the photo-emissive event has been commanded (column 1, liens 58-67). More specifically, Doblhofer teach an output triggered by the trailing flank of a light pulse resets the integrator of the photomultiplier (column 3, lines 25-35), and further teaches that this prevents spuriously arising dark current pulses from being sensed or counted (column1, lines 60-67) and also provides for a photon detection and counting system which is accurate, but requires little in the way of apparatus and does not require expensive highly accurate and rapid sophisticated electronic circuitry (column 1, lines 43-48).

Therefore it would have have been obvious to one of ordinary skill in the art to reset the photomultiplier of Liotta et al, as suggested by Doblhofer, in order to prevent spuriously arising dark current pulses from being sensed or counted, and also to provide for a photon detection and counting system which is accurate, but requires little in the way of apparatus and does not require expensive highly accurate and rapid sophisticated electronic circuitry.

While Liotta et al do not specifically teach that the calcium-sensitive luminescent material is selected to obtain a period of time between the flash emitted by the ultraviolet light source and the emission of light by the calcium-sensitive luminescent material, the calcium-

sensitive luminescent material used by Liotta et al is aequorin, which is what is used by applicants as the calcium-sensitive luminescent material, as seen in claim 7. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Therefore, the fact that the calcium-sensitive luminescent material is selected to obtain a period of time between the flash emitted by the ultraviolet light source and the emission of light by the calcium-sensitive luminescent material is not given any patentable weight, as the calcium-sensitive luminescent material is the same (aequorin).

5. With respect to claims 4, 5, and 6, Liotta et al teach the use of calcium chelating agents such as EDTA or EGTA during one or more pretreatment steps (column 12, lines 53-56), where the chelating agent could be incorporated into a sample collection device (column12, lines 60-65) which would act as a filter by removing free calcium. Liotta et al further teach that the sample can be blood (column 6, lines 1-15, column 12, lines 60-63).

6. With respect to claims 7, 17, Liotta et al teach that the photoprotein can be aequorin (column 9, lines 50-55).

7. With respect to claim 10, Liotta et al teach that the substrate can be comprised of nitrocellulose (column 11, lines 46-65).

8. With respect to claim 11, Liotta et al teach that the substrate comprises a transverse stripe with immobilized second binding partner and a calcium caging compound (column 12, lines 46-50, column 13, lines 15-45).

9. With respect to claim 12, Liotta et al teach that the calcium caging compound is loaded with an excess of calcium, in order to overcome any residual chelating agents from the pretreatment steps (column 13, lines 7-12).

10. With respect to claim 14, Liotta et al teach that the invention is an immunoassay device and utilizes antibodies (column 4, line 65-67) for binding to antigens (column 5, lines 40-65).

11. With respect to claims 15, 16, Liotta et al teach that the binding assay can be an immunoassay or a nucleic acid hybridization assay (column 5, line 38 – column 6, line 50).

12. With respect to claim 27, Liotta et al teach the use of calcium chelating agents such as EDTA prior to the pulse of ultraviolet light. Although Liotta et al do not specifically state that the solution contains less than 20 nM of calcium, they teach the use of EDTA to remove any calcium in the solution (column 13, lines 10-14) such that any calcium remaining would be of a concentration less than 20 nM.

13. With respect to claims 41, 46, Liotta et al teach the use of calcium chelating agents such as EDTA prior to the pulse of ultraviolet light. Although Liotta et al do not specifically state that the solution contains less than 20 nM of calcium, they teach the use of EDTA to remove any calcium in the sample (solution) such that for a sample containing 2 mmol of calcium it is diluted with 10 mmol EDTA (column 13, lines 10-14), which would result in free calcium concentration in the sample of less than 20 nmol.

14. Claims 2, 3, 21-25, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al [US 5,942,407], in view of Doblhofer [US 4,091,277], as applied to claim 1 above, and further in view of Pankratz et al [US 5,876,935].

With respect to claims 2, 21, 23, Liotta et al teach a method of using an immunoassay device comprises a sandwich arrangement of three, porous matrix layers (FIG. 1A). The first porous layer corresponds to the signal generating zone and is impregnated with a specific antibody (first binding partner) linked with a photoprotein or a suitable enzyme (label) (column 4, lines 65 – column 5, line 2). The second porous layer is the trapping zone, contains immobilized (bound) reference antigen (second binding partner) that is specifically recognized by the antibody in the first porous layer (column 5, lines 1-4). The third layer corresponds to the reporter system zone and contains a light emitting substance or activating agent that reacts with the photoprotein or enzyme linked to the antibody. Liotta et al further teach that the activating agent may be a caged calcium compound (column 13, lines 30-32) immobilized in a support and using ultraviolet light to activate the compound (column 13, lines 25-35), in order to extend the duration of light emission resulting from analyte detection (column 13, lines 35-40). Liotta et al further teach using a luminometer that is a compact photomultiplier for sensing the light (column 13, lines 49-53). Liotta et al fail to teach that the specific antibody (first binding partner) is immobilized on a paramagnetic particle or is biotinylated.

Pankratz et al teach a method comprising the steps of combining with a sample a binding reagent labeled with a luminescent molecule that is capable of binding to an analyte, contacting the sample with another binding reagent that can be biotinylated (column 5, lines 1-4), immobilized on a solid support such as superparamagnetic microspheres (column 7, example 2)

by means of avidin or streptavidin (column 5 lines 1-4) so that a complex with the analyte bound to the labeled binding reagent is formed, activating the luminescent label in the solid support-free sample or in the complex bound to the solid support, and determining the presence of analyte in the sample by detecting the light emitted from the activated luminescent label (claim 1). Pankratz et al further teach that the label can be aequorin, and is activated by adding sufficient calcium ions (column 5, line 65-column 6, lines 4). Pankratz et al further teach that the magnetic particles are preferred as mixing and separation steps can be conveniently and rapidly accomplished by application of a strong magnetic field (column 5, lines 31-40), and that particles have a high surface area that improves the efficiency and kinetics of the capture step (column 5, lines 10-31).

Therefore, it would have been obvious to one of ordinary skill in the art to have the specific antibodies of Liotta et al to be biotinylated at immoibilized to a solid support such as superparamagnetic microspheres, as suggested by Pankratz et al, such that mixing and separation steps in the method of Liotta et al can be conveniently and rapidly accomplished, as well as improving the efficiency and kinetics of the capture step.

15. With respect to claims 3, Pankratz et al teach that the method is an immunoassay for detecting and quantifying an antigen (column 1, lines 13-22). Liotta et al also teach that the invention is an immunoassay method that utilizes antibodies (column 4, line 65-67) for binding to antigens (column 5, lines 40-65).

16. With respect to claims 22, 24, Pankratz et al teach that all the component may be added at the same time, in which case the binding reactions would occur simultaneously (column 3, lines 40-45).

17. With respect to claims 42, 43 47, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranged involves only routine skill in the art. *In re Aller*, 105 USPQ 233. Therefore, it would have been obvious through normal optimization techniques known in the art to load the calcium-caging compound with up to 75% calcium.

18. With respect to claims 44, 45, Liotta et al teach the use of calcium chelating agents such as EDTA prior to the pulse of ultraviolet light. Although Liotta et al do not specifically state that the solution contains less than 20 nM of calcium, they teach the use of EDTA to remove any calcium in the sample (solution) such that for a sample containing 2 mmol of calcium it is diluted with 10 mmol EDTA (column 13, lines 10-14), which would result in free calcium concentration in the sample of less than 20 nmol.

19. Claims 8, 9, 13, 18, 20, 49, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al [US 5,942,407] in view of Doblhofer [US 4,091,277], and further in view of Ellis-Davies et al [US 5,446,186].

With respect to claims 13, 49, 52, Liotta et al and Doblhofer teach a method of a binding assay as discussed above involving the use of aequorin and obelin (column 13, lines 15-25) and of caged calcium compounds. Neither Pankratz et al nor Liotta et al disclose specific caged calcium compounds.

Ellies-Davies et al, however, teach that compounds such as 1-(4,5 dimethoxy-2-nitrophenyl)-1, 2 diaminoethane-N, N, N', N'-tetraacetic acid (DM-nitrophen) and nitrophenyl-ethylenebis(oxyethylenennitrilo) tetraacetic acid (NP-EGTA) are well known in the art as calcium chelating compounds (column 1, lines 50-60, column 2, lines 6-20). Ellies-Davies et al

further teach that the compounds produce very high yields of liberated Ca^{2+} (column 1, lines 57-61, column 2, lines 10-15).

Therefore, since Liotta et al teach aequorin and obelin, and further teach the use of a generic caged calcium compound, it would have been obvious to use a specific caged calcium compound such as DM-nitrophen or NP-EGTA in the method of Liotta et al, as suggested by Ellis-Davies et al, in order to obtain high yields of liberated Ca^{2+}.

20. With respect to claims 8, 9, 18, and 20, Liotta et al teach the use of ultraviolet light at (column 13, lines 30-35) which can be in the form of a light pulse (column 17, lines 24-25), to activate the caged calcium compound. Ellis-Davies et al further specify the use of a laser at 347 nm (column 8, lines 25-32) liberates the Ca^{2+}. Liotta et al further teach that a photomultiplier is used to sense the luminescence (column 13, lines 49-53), which in the case of aequorin would be at about 470 nm (column 9, lines 57).

21. Claims 50, 51, 53, 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al [US 5,942,407] in view of Doblhofer [US 4,091,277] and Pankratz et al [US 5,876,935], and further in view of Ellis-Davies et al [US 5,446,186].

With respect to claims 50, 51, 53, 54, Liotta et al and Doblhofer teach a method of a binding assay as discussed above involving the use of aequorin and obelin (column 13, lines 15-25) and of caged calcium compounds. Neither Pankratz et al nor Liotta et al disclose specific caged calcium compounds.

Ellies-Davies et al, however, teach that compounds such as 1-(4,5 dimethoxy-2-nitrophenyl)-1, 2 diaminoethane-N, N, N', N'-tetraacetic acid (DM-nitrophen) and nitrophenyl-ethylenebis(oxyethylenennitrilo) tetraacetic acid (NP-EGTA) are well known in the art as

calcium chelating compounds (column 1, lines 50-60, column 2, lines 6-20). Ellies-Davies et al further teach that the compounds produce very high yields of liberated Ca^{2+} (column 1, lines 57-61, column 2, lines 10-15).

Therefore, since Liotta et al teach aequorin and obelin, and further teach the use of a generic caged calcium compound, it would have been obvious to use a specific caged calcium compound such as DM-nitrophen or NP-EGTA in the method of Liotta et al, as suggested by Ellis-Davies et al, in order to obtain high yields of liberated Ca^{2+}.

Response to Arguments

Applicant's arguments filed December 30, 2005 have been fully considered but they are not persuasive. New rejections utilizing the same references, however, have been issued, in the hopes of clarifying the issues at hand as well as any misconceptions the applicants may have.

22. With respect to applicant's arguments on p. 7-8 that Liotta et al do not teach the use of a caged calcium compound, this is not found persuasive. Liotta et al specifically teach that caged calcium compounds may be used to release calcium from the dried zone, by the introduction of ultraviolet light (column 13, lines 30-34). With respect to applicant's arguments that Liotta et al merely speculates on the use of caged calcium compounds, applicant is directed to rejection above with respect to Liotta et al [US 5,942,407] in view of Doblhofer [US 4,091,277], and also to claims 1 and 2, where Liotta recites the use of "dried caged metal cation compound", where the metal cation is Ca^{2+}. With respect to applicant's arguments that Liotta et al do not consider any of the technical limitations or the problems to be overcome in supplying calcium in a caged form and releasing the calcium appropriately to activate calcium sensitive luminescent material, the Office notes that applicants have not addressed any of these issues either in the claims, and

have merely recited the limitation of "exposing said capture strip to a pulse of ultraviolet light to effect the release of calcium from the calcium-caging compound". Since Liotta et al do teach this particular step, applicant's arguments are found unpersuasive.

23. Applciant further argues in the response that Liotta et al make a vague suggestion that caged calcium compounds could be used, the Office again notes that Liotta et al in fact recites the use of "dried caged metal cation compound", where the metal cation is Ca^{2+} in claims 1 and 2. It is unclear how applicant would infer this to be a vague suggestion or mere speculation.

24. With respect to applicant's argument on p.10 that there is nothing in the teachings of Liotta et al which enable one of ordinary skill in the art to employ caged calcium compounds in an assay such as the assay described in Pankratz et al, it should be noted that with respect to claim 1, Liotta et al in fact teach the same assay as Pankratz et al, except with use of caged calcium compounds. The rejection of claim 1 has been rewritten to reflect this fact, specifically to remove the Pankratz reference which is unnecessary. Therefore, applicant's arguments that Liotta et al provide nothing more than mere speculation and provide no motivation is found unpersusasive as well as moot.

With respect to applicant's argument that Doblhofer is not relevant to the invention at hand and does not teach how to avoid interference between two different light sources, it should be noted as discussed above, that the integrating circuit of the PMT is disabled when no photon events are expected, and also that the integrator is reset after each light pulse. Therefore, there would be no interference between light pulses. Furthermore, even though Doblhofer provides a different motivation for resetting the PMT after each light pulse, as motivation for combining is still valid. Although applicant has recognized another advantage which would flow naturally

from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

25. With respect to applicant's arguments that Liotta et al teaches away from free calcium in the solution from being less than 20 nmol, this is not found persuasive, as Liotta et al specifically teach using 10 mmol of EDTA to dilute any calcium in the sample (solution).

26. With respect to applicant's arguments that Liotta et al teaches away from the calcium caging compound from being from being loaded up to 75% calcium, it is unclear how applicant came to such a conclusion. As applicant has pointed out, Liotta et al merely teach an excess of calcium to overcome the residual EDTA in the sample. Furthermore, the fact that Liotta et al teach the use of chelating compounds such as EDTA and calcium caging compounds in order to prevent the presence of free calcium that would cause premature activation of aequorin (column 13, lines 1-6). Therefore, the argument has not been found persuasive.

27. With respect to applicant's argument that Liotta et al defines calcium levels thought not achievable using calcium compounds without triggering premature light emission, no support for this statement could be found, and therefore the argument has not been found persuasive.

Conclusion

28. No claims are allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

30. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nelson Yang
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Art Unit 1641

BAO-THUY L. NGUYEN
PRIMARY EXAMINER
3/20/06